REMARKS

Claims 171-192 are pending and under consider in the present application. Claim 193 has been added. Claims 171, 178, and 191 have been amended. Claim 186 have been canceled, without prejudice.

No new matter has been added with the amendments and newly added claims. The amendments to claims 171 which recite using FACS, are supported for example, by page 45 lines 8-10. The amendment to claim 178 and newly added claim 193, which recite that the vector encodes a β-lactamase without a signal sequence are supported for example, by page 29, lines 18-26. The amendment to claim 191 cancels certain claim language. Upon entry of the present amendment, claims 171-185, and 187-193 will be pending and under consideration.

Rejection Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 171-192 under 35 U.S.C. § 103 as being unpatentable over Forrester et al. (*Proc. Natl. Acad. Sci.* 93:1677 (1996) in view of Tsien et al. (U.S. Pat. No. 5,741,657) and further in view Hicks et al. (*Meth. Enzymol.* 254:263 (1995)). The Office Action reasserts that Forrester et al. teach a plurality of clonal cells wherein each clonal cell includes a distinct fusion RNA of a cellular RNA transcript and a beta-galactosidase polynucleotide. Furthermore, the Office Action reasserts that the clonal cells of Forrester et al. exhibit as much as a 12.4-fold induction in beta-galactosidase expression in response to the induction of expression of the target in the clonal cells after exposure of the clonal cells to a ligand for the target.

The Office Action acknowledges that Forrester et al. do not teach the use of beta-lactamase in place of beta-galactosidase as the reporter. Furthermore, the Office Action indicates that it is unclear whether the vector of Forrester et al. is a viral vector. However, the Office Action reasserts that Tsien et al. teach the use of beta-lactamase in place of beta-galactosidase. Furthermore, the Office Action reasserts that Hicks et al. teach the use of a retroviral gene trap vector.

Regarding combining Tsien et al. with Forrester et al., the Office Action reasserts that it would have been obvious to modify the method of Forrester et al. to substitute the beta-lactamase enzyme of Tsien et al. for beta-galactosidase, since Tsien et al. allegedly teach that use of the novel beta-lactamase substrates provides distinct advantages over use of substrates for known reporter genes including beta-galactosidase because of the high efficiency, diffusion control, sensitivity, and detection within living cells of the beta-lactamase substrate. Regarding combining Hicks et al. with Forrester et al., the Office Action reiterates that statements in Hicks et al. indicate that retrovirus vectors are easier to use, especially for large scale mutagenesis, and the structure of the recombinant product is more predictable.

To establish a prima facie case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The patent office has the burden of establishing a prima facie case of obviousness. Id. The teaching or suggestion to make the claimed combination must be found in the prior art and not based on the Applicants' disclosure. MPEP § 706.02 citing In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991); MPEP § 2145, section XD.

Applicants reassert, as illustrated in Figure 1 of the present application, that the important advantages related to the pending claimed invention of using a membrane permeant beta-lactamase substrate over prior technologies such as those utilizing beta-galactosidase, include the ability to functionally screen immediately after the rapid identification of a functionally active portion of a genome without the necessity of transferring the identified portion of the genome into a secondary screening system and without the need to identify and grow clone stocks (Page 17, lines 8-15). The Office Action alleges that these features are not claim elements, and therefore cannot render the claims patentable over the cited art. However, the Applicant reasserts that without this teaching, there is no motivation to combine Tsien et al. with Forrester et al. and Hicks et al. Nevertheless, to expedite allowance of the pending claims, applicants have

amended independent claim 171 to recite that the cells were selected using fluorescence activated cell sorting (FACS). Furthermore, Applicants point out that pending claims 189 and 191 previously recited that the cells were selected using FACS. Therefore, these claims recite a process element that is directly related to an advantage of the present invention over the method of Forrester et al., and not simply functional language. By selecting cells using FACS, cells can be functionally assayed and isolated in a living state, from which they can be directly cultured. By using FACS to select cells that exhibit a change in β-lactamase expression, cells are rapidly identified without the need of a secondary screening system and without the need to identify and grow clone stocks. Using FACS to select cells of the clonal population is not taught or mentioned in Forrester et al., Tsien et al., or Hicks et al. In fact, it is not possible to use FACS with the detection system of Forrester et al. Therefore, these references do not teach all of the claim limitations of claims 171-177, 179-185, 189, and 191-193.

In addition, regarding claims 178 and 193, which recite that the clonal cells were selected from a population of cells transfected with a viral vector encoding a β-lactamase without a functional signal sequence, the cited references are silent regarding this element. As acknowledged in the Office Action, Forrester et al. and Hicks et al. are silent regarding a vector encoding a β-lactamase. Furthermore, Tsien et al. do not mention using a vector that encodes a β-lactamase without a functional signal sequence. Using a β-lactamase without a functional signal sequence is advantageous since this assures that when the nucleic acid encoding β-lactamase is encoded by a cell, more enzyme is available within the cell to cleave a cell membrane permeant substrate, thereby increasing the signal generated by a cell expressing the cytoplasmic β-lactamase. Furthermore, without a signal sequence, less β-lactamase is secreted into the extracellular medium to possibly contribute to background fluorescence.

Claims 185, 188, and 191 recite that the cells were selected using a membrane permeant β-lactamase substrate that is transformed by the cell into a membrane impermeant substrate. As indicated in the pending specification, transformation inside the cell to an impermeant substrate can occur via intracellular enzymes (e.g. esterases) or intracellular metabolites or organic molecules (e.g. sulfhydryl groups) (Page 52, lines 3-7. This transformation increases the

fluorescence generated inside a cell expressing β-lactamase, and should result in reduced background fluorescence as well. As acknowledged in the Office Action, Forrester et al. and Hicks et al. are silent regarding a β-lactamase substrate. Furthermore, Tsien et al. do not disclose that a β-lactamase substrate can be transformed by the cell into a membrane impermeant substrate, or the benefits of this transformation, especially when using FACS. In summary, since the recited references do no teach all of the claim elements, Applicants respectfully request withdrawal of the rejection of claims 171-191 under 35 U.S.C. § 103 as being unpatentable over Forrester et al. (*Proc. Natl. Acad. Sci.* 93:1677 (1996) in view of Tsien et al. (U.S. Pat. No. 5,741,657) and further in view Hicks et al. (*Meth. Enzymol.* 254:263 (1995)).

CONCLUSION

In view of the amendments and the above remarks, it is submitted that the application is in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355

Respectfully submitted,

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